

Application No.: 09/745920

Docket No.: 2007536-0038

**AMENDMENTS TO THE CLAIMS**

1. (Previously Presented) A method of determining the likelihood of the presence of a biomolecule in a sample comprising the steps of:
  - measuring a mass spectrum of one or more biomolecules from a sample to provide at least one mass signal corresponding to a biomolecule fragment of one or more of said biomolecules, wherein said mass signal has a mass signal intensity;
  - comparing said mass signal to a list of known biomolecule fragment signals to determine a potential source biomolecule of said mass signal, wherein said mass signal corresponds to at least one biomolecule fragment of said potential source biomolecule;
  - determining a biomolecule fragment score for said mass signal, wherein said biomolecule fragment score comprises a function of:
    - the mass signal intensity for said mass signal,
    - a biomolecule fragment detection parameter for a biomolecule fragment of said potential source biomolecule, said biological fragment detection parameter for said biomolecule fragment comprises a numerical value that is a measure of the likelihood of detecting the biomolecule fragment as a fragment, digestion product, or both, of said potential source biomolecule, the likelihood of detecting said biological fragment being based at least in part on relative mass signal intensity relationships between biomolecule fragments, fractions of biomolecule fragments, or both; and
    - a mass error for said mass signal from the relative difference between a mass which corresponds to said mass signal and a mass of the biomolecule fragment;

Application No.: 09/745920

Docket No.: 2007536-0038

repeating the steps of comparing and determining a biomolecule fragment score for additional mass signals;

combining said biomolecule fragment scores of said mass signals that correspond to a known biomolecule fragment list for said potential source biomolecule, said combination defining a biomolecule score for said potential source biomolecule;

repeating the step of combining as necessary for additional potential source biomolecules; and

determining the likelihood of the presence or absence of a biomolecule in the sample based on a comparison of said biomolecule score of said potential source biomolecule that corresponds to said biomolecule to at least one other biomolecule score.

2. (Original) The method of claim 1 wherein the step of determining the likelihood of the presence or absence of said biomolecule further comprises the steps of:

selecting one of said at least one mass signal, which defines a selected mass signal;

comparing said biomolecule scores of at least two potential source biomolecules that correspond to said selected mass signal to determine said potential source biomolecule with a highest biomolecule score;

determining that said biomolecule is likely absent if said biomolecule score of the corresponding potential source biomolecule is lower than said highest biomolecule score; and

repeating the steps of selecting, comparing biomolecule scores and determining as necessary for additional selected mass signals.

Application No.: 09/745920

Docket No.: 2007536-0038

3. (Original) The method of claim 1 further comprising the step of correcting said mass signal intensity for an isotopic variant of a biomolecule fragment which corresponds to said mass signal.
4. (Original) The method of claim 1 further comprising the step of calibrating a mass which corresponds to said mass signal.
5. (Original) The method of claim 1 further comprising the step of removing noise from said mass signal intensity.
6. (Original) The method of claim 1 further comprising the step of removing artificial background intensity from said mass signal intensity.
7. (Original) The method of claim 1 wherein said biomolecule fragment detection parameter is proportional to the detection efficiency of said biomolecule fragment that corresponds to said mass signal and a probability that said potential source biomolecule yields said biomolecule fragment as a result of fragmentation process applied to said potential source biomolecule.
8. (Canceled)
9. (Previously Presented) The method of claim 1 wherein said biomolecule fragment score is proportional to said biomolecule fragment detection parameter and said mass signal intensity, and inversely proportional to said mass error for said mass signal.

Application No.: 09/745920

Docket No.: 2007536-0038

10. (Original) The method of claim 1 wherein the step of combining said biomolecule fragment scores comprises excluding a selected biomolecule fragment score from said combination.
11. (Previously Presented) The method of claim 1 wherein the step of combining said biomolecule fragment scores further comprises the steps of:
  - determining a biomolecule fragment count of said potential source biomolecule by counting the number of said mass signals that correspond to said potential source biomolecule;
  - comparing said biomolecule fragment count to the number of said biomolecule fragments on a known biomolecule fragment list for said potential source biomolecule to determine a relative biomolecule match count for said potential source biomolecule;
  - calculating a weighted biomolecule score for said potential source biomolecule from said biomolecule score and said relative biomolecule match count; and
  - wherein the step of determining the likelihood of the presence or absence of said biomolecule comprises determining the likelihood of the presence or absence of said biomolecule based on a comparison of said weighted biomolecule score of said potential source biomolecule that corresponds to said biomolecule to at least one other weighted biomolecule score.
12. (Original) The method of claim 1 wherein the step of determining the likelihood of the presence or absence of said biomolecule further comprises the steps of:

Application No.: 09/745920

Docket No.: 2007536-0038

determining a biomolecule fragment count of said potential source biomolecule by counting the number of said mass signals that correspond to said potential source biomolecule; and

determining that said biomolecule is likely absent if said biomolecule fragment count of the corresponding potential source biomolecule is lower than a minimum number.

13. (Original) The method of claim 1 wherein the step of determining the likelihood of the presence or absence of said biomolecule further comprises the steps of:

determining a mass error for said mass signal from the relative difference between a mass which corresponds to said mass signal and a mass of a known biomolecule fragment which corresponds to said mass signal;

repeating the step of determining a mass error as necessary for additional mass signals that correspond to a known biomolecule fragment list for said potential source biomolecule;

selecting a mass tolerance value; and

determining that said biomolecule is likely absent if more than an insignificant number of said mass signals that correspond to said biomolecule have a said mass error that is greater than said selected mass tolerance value.

14. (Original) The method of claim 1 wherein the step of determining the likelihood of the presence or absence of said biomolecule further comprises the steps of:

identifying from about 100 to about 200 of the most intense mass signal intensities to determine the intense mass signals;

Application No.: 09/745920

Docket No.: 2007536-0038

determining an intense biomolecule fragment count of said potential source biomolecule by counting the number of said intense mass signals that correspond to said potential source biomolecule; and

determining that said biomolecule is likely absent if said intense biomolecule fragment count of the corresponding potential source biomolecule is lower than a minimum number.

15. (Previously Presented) The method of claim 14 wherein the step of identifying comprises:

determining a mass error for said mass signal from the relative difference between a mass which corresponds to said mass signal and a mass of a known biomolecule fragment which corresponds to said mass signal;

selecting a mass tolerance value; and

identifying from about 100 to about 200 of the most intense mass signals with a said mass error less than said mass tolerance value and a biomolecule fragment detection parameter greater than a minimum number to determine the intense mass signals.

16. (Original) The method of claim 1 further comprising the step of determining a relative concentration of said biomolecule based on said biomolecule score.

17. (Previously Presented) The method of claim 1, wherein the step of combining said biomolecule fragment scores comprises:

combining at least two of said mass signal intensities to determine a signal intensity score;

Application No.: 09/745920

Docket No.: 2007536-0038

combining said mass signal intensities of said mass signals which correspond to said known biomolecule fragment list for said potential source biomolecule to determine a potential source biomolecule intensity score;

comparing said signal intensity score to said potential source biomolecule intensity source to determine a relative biomolecule intensity corresponding to said potential source biomolecule;

calculating a weighted biomolecule score for said potential source biomolecule from said biomolecule score and said relative biomolecule intensity; and

wherein the step of determining the likelihood of the presence or absence of said biomolecule comprises determining the likelihood of the presence or absence of said biomolecule based on a comparison of said weighted biomolecule score of said potential source biomolecule that corresponds to said biomolecule to at least one other weighted biomolecule score.

18. (Previously Presented) The method of claim 1, wherein the step of combining said biomolecule fragment scores comprises:

combining at least two of said biomolecule fragment scores to determine a signal biomolecule fragment score;

comparing said signal biomolecule fragment score to a said potential source biomolecule score to determine a relative biomolecule detection parameter corresponding to said potential source biomolecule;

calculating a weighted biomolecule score for said potential source biomolecule from said biomolecule score and said relative biomolecule detection parameter; and

Application No.: 09/745920

Docket No.: 2007536-0038

wherein the step of determining the likelihood of the presence or absence of said biomolecule comprises determining the likelihood of the presence or absence of said biomolecule based on a comparison of said weighted biomolecule score of said potential source biomolecule that corresponds to said biomolecule to at least one other weighted biomolecule score.

19. (Previously Presented) The method of claim 1, wherein the step of combining said biomolecule fragment scores comprises:

determining a mass error for said mass signal from the relative difference between a mass which corresponds to said mass signal and a mass of a known biomolecule fragment which corresponds to said mass signal;

repeating the step of determining a mass error as necessary for additional mass signals that correspond to a known biomolecule fragment list for said potential source biomolecule;

combining said mass errors for said mass signals corresponding to said potential source biomolecule to determine a biomolecule mass error for said potential source biomolecule;

repeating the steps determining a mass error and combining said mass errors as necessary for additional potential source biomolecules;

calculating a weighted biomolecule score for a potential source biomolecule from the biomolecule score and biomolecule mass error of the potential source biomolecule; and

wherein the step of determining the likelihood of the presence or absence of said biomolecule comprises determining the likelihood of the presence or absence of said



Application No.: 09/745920

Docket No.: 2007536-0038

biomolecule based on a comparison of said weighted biomolecule score of said potential source biomolecule that corresponds to said biomolecule to at least one other weighted biomolecule score.

20. (Original) The method of claim 19 wherein the step of combining said mass errors further comprises weighting a said mass error by the corresponding mass signal intensity to determine a weighted mass error and combining said weighted mass errors to determine said combined biomolecule mass error.
21. (Original) The method of claim 1 wherein said step of determining the likelihood of the presence or absence of said biomolecule comprises determining the likelihood of the presence or absence of a protein.
22. (Original) The method of claim 1 wherein said step of comparing said mass signals to a list of known biomolecule fragments signals comprises comparing said mass signals to a list of all known peptides.
23. (Currently Amended) A method of determining the likelihood of the presence of a biomolecule in a sample comprising the steps of:  
  
measuring a mass spectrum of one or more biomolecules from a sample to provide at least one mass signal corresponding to a biomolecule fragment of one or more of said biomolecules, wherein said mass signal has a mass signal intensity;

Application No.: 09/745920

Docket No.: 2007536-0038

comparing said mass signal to a list of known biomolecule fragment signals to determine a potential source biomolecule of said mass signal, wherein said mass signal corresponds to at least one biomolecule fragment of said potential source biomolecule;

determining a biomolecule fragment score for said mass signal, wherein the step of determining the biological fragment score comprises the steps of: said biomolecule fragment score comprises a function of:

determining a detection likelihood for said mass signal which defines a biomolecule fragment detection parameter; the mass signal intensity for said mass signal; a biomolecule fragment detection parameter for a biomolecule fragment of said potential source biomolecule, said biological fragment detection parameter for said biomolecule fragment comprises a numerical value that is a measure of the likelihood of detecting the biomolecule fragment as a fragment, digestion product, or both, of said potential source biomolecule, the likelihood of detecting said biological fragment being based at least in part on relative mass signal intensity relationships between biomolecule fragments, fractions of biomolecule fragments, or both;

determining a mass error for said mass signal from the relative difference between a mass which corresponds to said mass signal and a mass of a known biomolecule fragment which corresponds to said mass signal; and

determining said biomolecule fragment score from said mass signal intensity, said biomolecule fragment detection parameter, and said mass error for said mass signal; a mass error for said mass signal from the relative difference between a mass which corresponds to said mass signal and a mass of the biomolecule fragment;

Application No.: 09/745920

Docket No.: 2007536-0038

repeating the steps of comparing and determining a biomolecule fragment score for additional mass signals;

combining said biomolecule fragment scores of said mass signals that correspond to a known biomolecule fragment list for said potential source biomolecule, said combination defining a biomolecule score for said potential source biomolecule;

repeating the step of combining as necessary for additional potential source biomolecules; and

determining whether one or more mass signal mass ranges should be subjected to tandem mass spectrometry ("MS-MS") analysis based on said biomolecule score of said potential source biomolecule.

24. (Original) The method of claim 23 wherein said biomolecule fragment detection parameter is proportional to the detection efficiency of said biomolecule fragment that corresponds to said mass signal and a probability that said potential source biomolecule yields said biomolecule fragment as a result of fragmentation process applied to said potential source biomolecule.
25. (Canceled)
26. (Previously Presented) The method of claim 23 wherein said biomolecule fragment score is proportional to said biomolecule fragment detection parameter and said mass signal intensity, and inversely proportional to said mass error for said mass signal.

Application No.: 09/745920

Docket No.: 2007536-0038

27. (Original) The method of claim 23 wherein the step of combining said biomolecule fragment scores comprises excluding a selected biomolecule fragment score from said combination.
28. (Original) An article of manufacture having computer-readable program means for performing the method of claim 1 embodied thereon.
29. (Original) An article of manufacture having computer-readable program means for performing the method of claim 23 embodied thereon.
30. (Withdrawn) An apparatus for determining the likelihood of the presence of a biomolecule based on biomolecule fragment detection likelihood, the apparatus comprising:
- a biomolecule fragment separation apparatus providing at least one mass signal, wherein said mass signal has a mass signal intensity;
  - a first memory element storing said mass signal provided by said biomolecule fragment separation apparatus;
  - a second memory element storing a list of known biomolecule fragment signals;
  - a third memory element storing a comparator accessing said first memory element and said second memory element to determine if a mass signal stored in said first memory element matches a biomolecule fragment signal in said second memory element;
  - a fourth memory element storing a mass signal-biomolecule fragment signal match determined by said comparator;

Application No.: 09/745920

Docket No.: 2007536-0038

a fifth memory element containing a weight generator accessing said first memory element and said fourth memory element for determining a biomolecule fragment score for said mass signal;

a sixth memory element storing the biomolecule fragment scores;

a seventh memory element containing a combination generator accessing said third memory element and said sixth memory element for combining said biomolecule fragment scores of said mass signals that correspond to a known biomolecule fragment list for a potential source biomolecule; said combination defining a biomolecule score for said potential source biomolecule; and

an output device providing an output display of at least one of said biomolecule scores.

31. (Withdrawn) The apparatus of claim 30 wherein said biomolecule fragment separation apparatus comprises a MALDI ionization instrument.
32. (Withdrawn) The apparatus of claim 30 wherein said biomolecule fragment separation apparatus comprises a time-of-flight mass spectrometer.
33. (Withdrawn) The apparatus of claim 30 wherein said output device comprises a computer.